Kongeriget Danmark

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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

12 November 2003

Bo Zillo Tidemann

PATENT- OG VAREMÆRKESTYRELSEN

1,2,4-triaminobenzene derivatives

Field of the invention

The present invention relates to novel 1,2,4-triaminobenzene derivatives being openers of the KCNQ family potassium channels. The compounds are useful for the prevention, treatment and inhibition of disorders of the central nervous system.

Background of the invention

Ion channels are cellular proteins that regulate the flow of ions, including potassium, calcium, chloride and sodium into and out of cells. Such channels are present in all animal and human cells and affect a variety of processes including neuronal transmission, muscle contraction, and cellular secretion.

Humans have over 70 potassium channelsubunits (Jentsch *Nature Reviews Neuroscience* 2000, 1, 21-30) with a great diversity with regard to both stucture and function. Neuronal potassium channels, which are found in the brain, are primarily responsible for maintaining a negative resting membrane potential, as well as controlling membrane repolarisation following an action potential.

One subset of potassium channel genes is the KCNQ family. Mutations in four out of five KCNQ genes have been shown to underlie diseases including cardiac arrthymias, deafness and epilepsy (Jentsch *Nature Reviews Neuroscience* 2000, 1, 21-30). The KCNQ4 gene is thought to encode the molecular correlate of potassium channels found in outer hair cells of the cochlea and in Type I hair cells of the vestibular apparatus, mutations in which lead to a form of inherited deafness. KCNQ1 (KvLTQ1) is co-assembled with the product of the KCNE1 (minimal K(+)-channel protein) gene in the heart to form a cardiac-delayed rectifier-like K(+) current. Mutations in this channel can cause one form of inherited long QT syndrome (LQT1), as well as being associated with a form of deafness (Robbins *Pharmacol Ther* 2001, 90, 1-19).

The genes KCNQ2 and KCNQ3 were discovered in 1988 and appear to be mutated in a rare inherited form of benign familial neonatal convulsions (Rogawski *Trends in Neurosciences* 2000, 23, 393-398). The proteins encoded by the KCNQ2 and KCNQ3

genes are localised in the pyramidal neurons of the human cortex and hippocampus, regions of the brain associated with seizure generation and propagation (Cooper et al. *Proceedings National Academy of Science U S A* 2000, 97, 4914-4919).

KCNQ2 and KCNQ3 are two potassium channel subunits that form "M-currents" when expressed in vitro. The M-current is a non-inactivating potassium current found in many neuronal cell types. In each cell type, it is dominant in controlling membrane excitability by being the only sustained current in the range of action potential initiation (Marrion *Annual Review Physiology* 1997, 59, 483-504). Modulation of the M-current has dramatic effects on neuronal excitability, for example activation of the current will reduce neuronal excitability.

Retigabine (D-23129; N-(2-amino-4-(4-fluorobenzylamino)-phenyl) carbamic acid ethyl ester) and analogues thereof are disclosed in EP554543. Retigabine is an antiepileptic compound with a broad spectrum and potent anticonvulsant properties, both in vitro and in vivo. It is active after oral and intraperitoneal administration in rats and mice in a range of anticonvulsant tests including: electrically induced seizures, seizures induced chemically by pentylenetetrazole, picrotoxin and N-methyl-D-aspartate (NMDA) and in a genetic animal model, the DBA/2 mouse (Rostock et al. *Epilepsy Research* 1996, 23, 211-223). In addition, retigabine is active in the amygdala kindling model of complex partial seizures, further indicating that this compound has potential for antiepileptic therapy. In clinical trials, retigabine has recently shown effectiveness in reducing the incidence of seizures in epileptic patients (Bialer et al. *Epilepsy Research* 2002, 51, 31-71).

Retigabine has been shown to activate a K(+) current in neuronal cells and the pharmacology of this induced current displays concordance with the published pharmacology of the M-channel, which recently was correlated to the KCNQ2/3 K(+) channel heteromultimere. This suggests that activation of KCNQ2/3 channels may be responsible for some of the anticonvulsant activity of this agent (Wickenden et al. *Molecular Pharmacology* 2000, 58, 591-600) – and that other agents working by the same mechanism may have similar uses.

KCNQ channels have also been reported to be upregulated in models of neuropathic pain (Wickenden et al. *Society for Neuroscience Abstracts* 2002, 454.7), and

potassium channel modulators have been hypothesised to be active in both neuropathic pain and epilepsy (Schroder et al. *Neuropharmacology* 2001, 40, 888-898).

Finally, retigabine and KCNQ modulators may exhibit protection against the neurodegenerative aspects of epilepsy, as retigabine has been shown to prevent limbic neurodegeneration and the expression of markers of apoptosis following kainic acid-induced status epilepticus in the rat (Ebert et al. *Epilepsia* 2002, 43 Suppl 5, 86-95). This may have relevance for preventing the progression of epilepsy in patients, i.e. be anti-epileptogenic. Retigabine has also been shown to delay the progression of hippocampal kindling in the rat, a further model of epilepsy development (Tober et al. *European Journal Of Pharmacology* 1996, 303, 163-169).

WO01/022953 describes the use of retigabine for prophylaxis and treatment of neuropathic pain such as allodynie, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie and neupathic pain related to migraine.

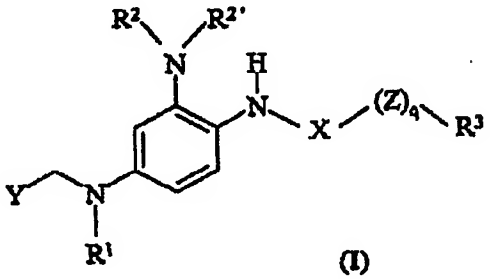
WO02/049628 describes the use of retigabine for the prevention, treatment, inhibition and amelioration of anxiety disorders such as anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias.

WO97/15300 describes the use of retigabine for the treatment of neurodegenerative disorders such as alzheimer's disease, huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-induced encephalopathy and other infection-related encephalopathies being caused by rubella viruses, herpes viruses, borrelia and by unknown pathogens, Creutzfeld-Jakob disease, Parkinson's disease, trauma-induced neurodegenerations, and neuronal hyperexcitation states such as in medicament withdrawal or by intoxication, neurodegenerative disorders of the peripheral nervous system such as polyneuropathies and polyneuritides.

Hence there is a great desire for novel compounds, which are potent openers of the KCNQ family potassium channels.

Summary of the invention

Accordingly, the present invention relates to novel 1,2,4-triaminobenzene derivative of formula I



(I)

wherein

R^1 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl;

R^2 and $R^{2'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, aryl, , C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

R^3 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, aryl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

X is CO or SO_2;

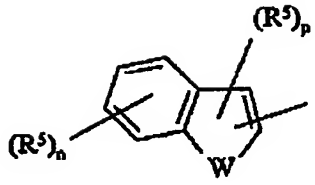
Z is O or NR^4, wherein R^4 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

q is 0 or 1;

and

Y represents a heteroaryl of formula II or III

II



III

wherein

W is O or S;

m is 0,1, 2 or 3;

n is 0, 1, 2, 3 or 4;

p is 0 or 1; and

each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, aryl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn)yl, acyl, halogen, halo-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8, SO_2OR^8;

wherein

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and aryl;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl and acyl; and

R^8 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

or pharmaceutically active acid addition salts thereof.

In one preferred embodiment, the invention relates to such compounds wherein R^1 is selected from the group consisting of hydrogen and C_{1-6}-alk(en/yn)yl.

In another embodiment, the invention relates to such compounds wherein at least one of the substituents R^2 and $R^{2'}$ is a hydrogen atom.

In yet another embodiment, the invention relates to such compounds, wherein both R^2 and $R^{2'}$ are hydrogen atoms.

In yet another embodiment, the invention relates to such compounds wherein R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl and aryl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to such compounds wherein R^3 is C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to such compounds wherein each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, halogen and $-SO_2R^8$ wherein R^8 is aryl.

In yet another embodiment, the invention relates to such compounds wherein X is CO.

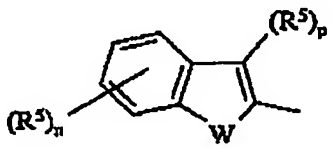
In yet another embodiment, the invention relates to such compounds wherein Z is an oxygen atom.

In yet another embodiment, the invention relates to such compounds wherein W is an oxygen atom.

In yet another embodiment, the invention relates to such compounds wherein W is a sulfur atom.

In yet another embodiment, the invention relates to such compounds wherein Y is of formula IIb or IIIb

IIb



IIIb

wherein W, m, n, p and R^5 are as defined above.

In yet another embodiment, the invention relate to such compounds wherein Y is of the below formula IIb^1, IIb^2, IIb^3, $IIIb^1$, $IIIb^2$, $IIIb^3$ or $IIIb^4$:

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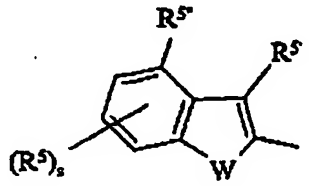
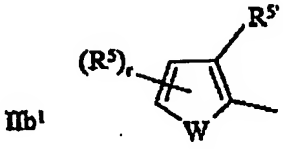
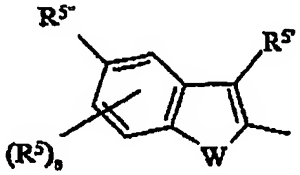
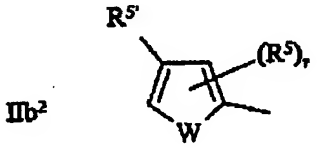
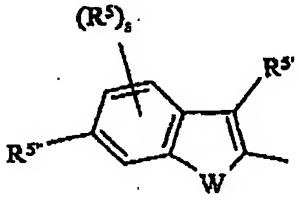
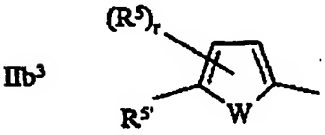

IIIb¹

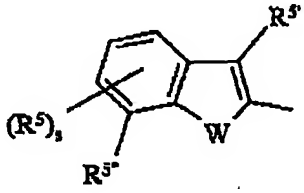

IIb¹


IIIb²


IIb²

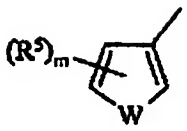

IIIb³


IIb³

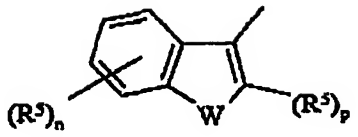

IIIb⁴

wherein W is as defined above; r is 0, 1 or 2; s is 0, 1, 2 or 3; and $R^{5'}$ and $R^{5''}$ are independently defined as R^5 and each R^5 is independently as defined above.

In yet another embodiment, the invention relates to such compounds wherein Y is of formula IIc or IIIc



IIc



IIIc

wherein W, m, n, p and R^5 are as defined above.

In yet another embodiment, the invention relates to such compounds wherein Y is of the below formula IIc^1, IIc^2, IIc^3, $IIIc^1$, $IIIc^2$, $IIIc^3$ or $IIIc^4$:

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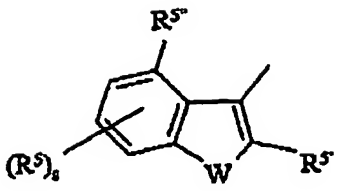
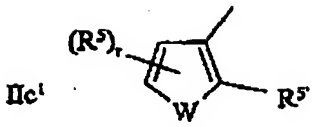
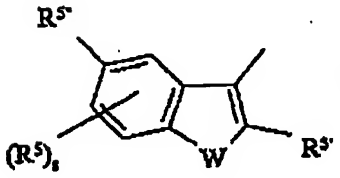


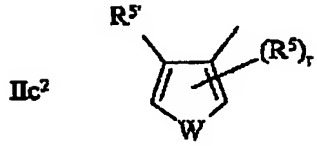
IIIc1



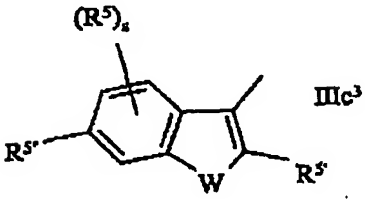
IIc1



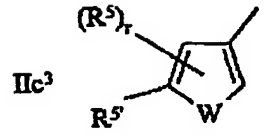
IIIc2



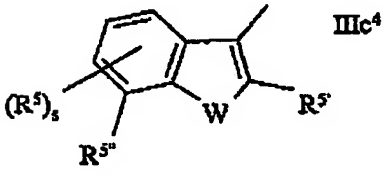
IIc2



IIIc3



IIc3



IIIc4

wherein W is as defined above; r is 0, 1 or 2; s is 0, 1, 2 or 3; and $R^{5'}$ and $R^{5''}$ are independently defined as R^5 and each R^5 is independently as defined above.

In yet another embodiment, the invention relates to such compounds wherein Y is of formula II.

In yet another embodiment, the invention relate to such compounds wherein Y is of formula III.

The compounds of the following list and pharmaceutically acceptable acid addition salt thereof are preferred:

3b {2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-methyl-amino]-phenyl}-carbamic acid ethyl ester;

4a {2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

3a {2-Amino-4-[(5-methyl-thiophen-2-ylmethyl)-methyl-amino]-phenyl}-carbamic acid ethyl ester;

4b {2-Amino-4-[(5-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

2d {2-Amino-4-[(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

4e {2-Amino-4-[(benzo[b]thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

1b {2-Amino-4-[(5-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

2c {2-Amino-4-[(4-bromo-3-methoxy-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

4f {2-Amino-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

2b {2-Amino-4-[(3-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

2a (2-Amino-4-{[4-(4-chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-phenyl)-carbamic acid ethyl ester;

1c {2-Amino-4-[(3-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

1a {2-Amino-4-[(5-fluoro-benzofuran-3-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

1d {2-Amino-4-[(thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

4c {2-Amino-4-[(4-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

4d {2-Amino-4-[(5-ethyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

Ie {2-Amino-4-[(thiophen-3-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;
3c {2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-ethyl-amino]-phenyl}-carbamic acid ethyl ester.

The compounds of the invention have been found to have effect on potassium channels of the KCNQ family, in particular on the KCNQ2 subunit.

Accordingly, the compounds of the invention are considered to be useful in preventing, treating or inhibiting a variety of disorders of the central nervous system such as seizure disorders such as convulsions, epilepsy and status epilepticus; neuropathic pain such as allodynie, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie and neupathic pain related to migraine; anxiety disorders such as anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias; neurodegenerative disorders such as alzheimer's disease, huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-induced encephalopathy and other infection-related encephalopathies being caused by rubella viruses, herpes viruses, borrelia and by unknown pathogens, Creutzfeld-Jakob disease, Parkinson's disease, trauma-induced neurodegenerations, and neuronal hyperexcitation states such as in medicament withdrawal or by intoxication, neurodegenerative disorders of the peripheral nervous system such as polyneuropathies and polyneuritides.

According to one aspect, the compounds of the invention are considered to be useful in preventing, treating or inhibiting a variety of disorders of the central nervous system such as seizure disorders such as convulsions, epilepsy and status epilepticus; anxiety disorders such as anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias.

According to one particular aspect, the compounds of the invention are considered to be useful in preventing, treating or inhibiting seizure disorders such as convulsions, epilepsy and status epilepticus.

Thus, in one aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula I as defined above or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

Halogen means fluoro, chloro, bromo or iodo.

The expression C_{1-6}-alk(en/yn)yl means a C_{1-6}-alkyl, C_{2-6}-alkenyl or a C_{2-6}-alkynyl group.

The term C_{1-6}-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6}-alkenyl and C_{2-6}-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The expression C_{3-8}-cycloalk(en)yl means a C_{3-8}-cycloalkyl- or cycloalkenyl group.

The term C_{3-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C_{3-8}-cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

In the term C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{1-6}-alk(en/yn)yl are as defined above.

The term aryl refers to aromatic systems such as phenyl, naphtyl, thiophene and furan optionally being substituted with one or more substituents independently being hydroxy, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, C_{1-6}-alkoxy, C_{3-8}-alkoxy, acyl, nitro or cyano, -CO-NH-C_{1-6}-alk(en/yn)yl, -CO-N(C_{1-6}-alk(en/yn)yl)$_2$, -NH-C_{1-6}-alk(en/yn)yl, -N(C_{1-6}-alk(en/yn)yl)$_2$, -S- C_{1-6}-alk(en/yn)yl, -SO_2-C_{1-6}-alk(en/yn)yl and -SO_2O-C_{1-6}-alk(en/yn)yl.

As used herein, the term acyl refers to formyl, C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)ylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alk(en/yn)ylcarbonyl or a C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-carbonyl group, wherein C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and aryl are as defined above.

The term halo-C_{1-6}-alk(en/yn)yl designates C_{1-6}-alk(en/yn)yl being substituted with one or more halogen atoms, including but not limited to trifluormethyl.

The terms hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn), C_{1-6}-alk(en/yn)yloxy, C_{3-8}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-alk(en/yn)ylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)ylcarbonyl etc. designate such groups in which the C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and aryl are as defined above.

The acid addition salts of the invention are preferably pharmaceutically acceptable salts of the compounds of the invention formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

Pharmaceutical compositions

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents

comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg. The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

Preparation of the compounds of the invention

The compounds of the invention of the general formula I,
wherein R^1, R^2, $R^{2'}$, R^3, X, Z, and q are as defined above
are prepared by the methods as represented in the scheme and as described below:

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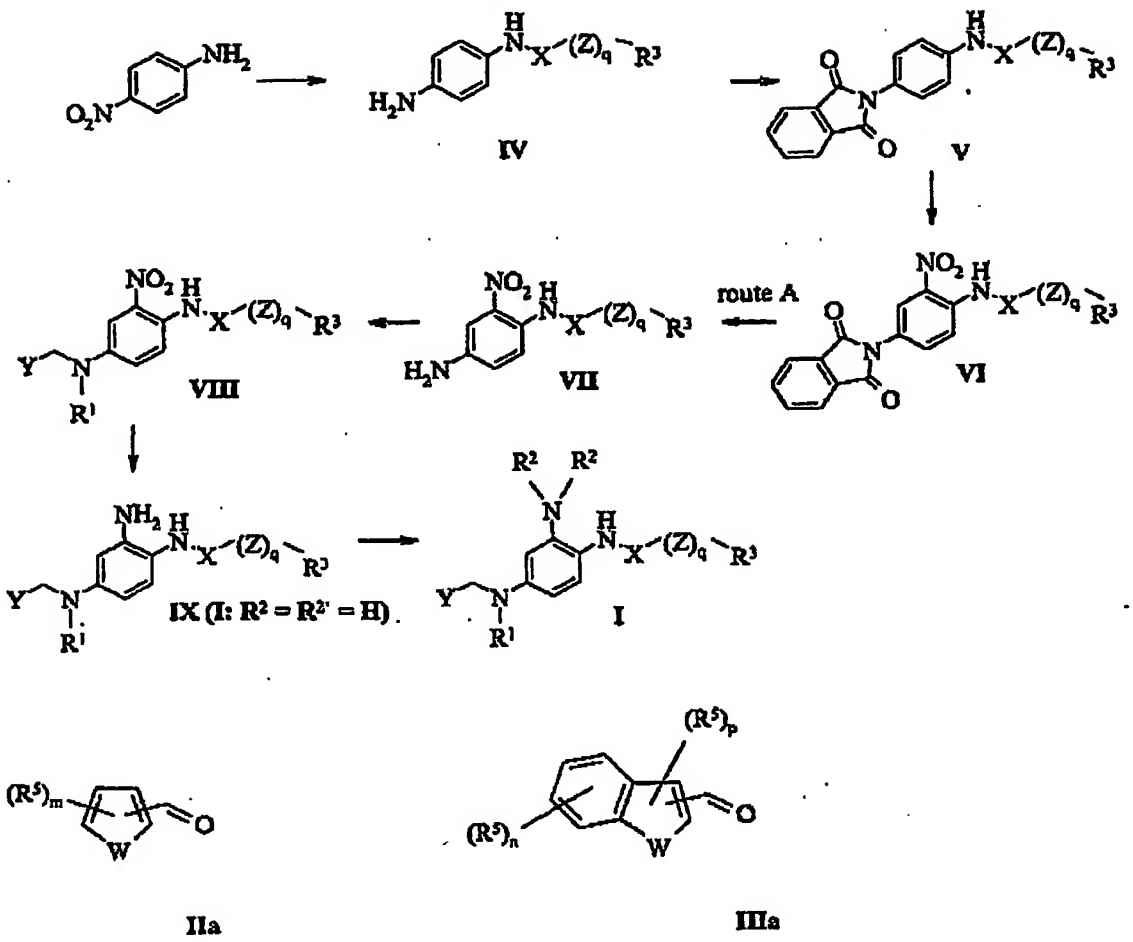


Compounds of the general formula VII are prepared according to methods known to chemists skilled in the art (v. Bebenburg et al. *Chemiker Zeitung* 1979, Sonderdruck 103, 3-15) and as outlined below:

Compounds of the general formula IV are prepared by the reaction of 4-nitroaniline with suitable electrophilic reagents, such as acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, and alkyl formiates with or without the addition of bases, such as trialkyl amines, potassium carbonate, or lithium-, sodium-, or potassium alcoholates, in a suitable solvent, such as ethyl acetate, dioxane, tetrahydrofuran, or diethyl ether, at a suitable temperature, such as room temperature or reflux

temperature, followed by reduction of the nitro group with a suitable reducing agent such as iron or zinc powder in aqueous hydrochloric acid or hydrogen gas in the presence of a suitable hydrogenation catalyst such as palladium on activated carbon in suitable solvents such as methanol or ethanol, at a suitable temperature.

Compounds of the general formula V are prepared by the reaction of compounds of the general formula IV with a reagent forming a protecting group on the aniline group, for example phthalic anhydride, in a suitable solvent, such as glacial acetic acid, at a suitable temperature.

Compounds of the general formula VI are prepared from compounds of the general formula V by nitration reactions known to the chemist skilled in the art, such as reaction with fuming nitric acid, in a suitable solvent, such as glacial acetic acid, at a suitable temperature.

Compounds of the general formula VII are prepared from compounds of the general formula VI by deprotection of the aniline function with hydrazine hydrate in a suitable solvent, such as 1,2-dioxane, at a suitable temperature.

Preparation of compounds of the general formula VIII:

Compounds of the general formula VII are subjected to reductive alkylation reactions, known to the chemist skilled in the art, with aldehydes of the general formulae IIa or IIIa using reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, THF, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, to form compounds of the general formula VIII, wherein R^1 is hydrogen.

Alternatively, compounds of the general structure VII can be reacted with aldehydes of the general structures IIa or IIIa in a suitable solvent, such as methanol, ethanol, THF, dioxane, xylene, or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid or acidic ion exchange resin, at a suitable temperature, to form imines, that can be isolated by crystallisation or by evaporation

of the solvent. The imines can then be reduced using reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, THF, water, dioxane or mixtures thereof, to compounds of the general formula **VIII**, wherein R^1 is hydrogen.

Optionally, for variation of R^1, the obtained compounds of the general formula **VIII** can be subjected to an additional reductive alkylation procedure using suitable aldehydes and reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, THF, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature as described above. This procedure can also be carried out *in-situ* after the first reductive alkylation with aldehydes of the general structures **IIa** or **IIIa**.

Alternatively, for variation of R^1, the obtained compounds of the general formula **VIII** can be subjected to an acylation reaction using suitable electrophilic reagents, such as acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, and alkyl formiates with the addition of bases, such as trialkyl amines, potassium carbonate, or lithium-, sodium-, or potassium alcoholates, in a suitable solvent, such as ethyl acetate, dioxane, tetrahydrofuran, or diethyl ether, at a suitable temperature, as described above.

Compounds of the general formula **IX**, are formed by reduction of compounds of the general formula **VIII** with a suitable reducing agent such as iron or zinc powder in aqueous hydrochloric acid or hydrogen gas in the presence of a suitable hydrogenation catalyst such as palladium on activated carbon in suitable solvents such as methanol or ethanol, at an suitable temperature. The resulting compounds are identical to compounds of the invention of the general formula **I**, wherein R^2 and $R^{2'}$ are hydrogen, and wherein R^1,R^3, X, Z, and q are as defined above.

Compounds of the general formula **I**, wherein R^1 is not hydrogen, and where R^2 and optionally $R^{2'}$ are not hydrogen, are obtained by the reaction of compounds of the general formula **IX**, wherein R^1 is not hydrogen, by using the following methods:

Introduction of R^2 by a reductive alkylation procedure using suitable aldehydes and reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, THF, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, as described above.

Optionalintroduction of $R^{2'}$ by an additional reductive alkylation procedure using suitable aldehydes and reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, THF, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, as described above.

Alternatively, $R^{2'}$ or R^2 is introduced by an acylation reaction using suitable electrophilic reagents, such as acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, and alkyl formiates with the addition of bases, such as trialkyl amines, potassium carbonate, or lithium-, sodium-, or potassium alcoholates, in a suitable solvent, such as ethyl acetate, dioxane, tetrahydrofuran, or diethyl ether, at a suitable temperature, as described above.

To obtain compounds of the general formula I, where R^1 is hydrogen, and where R^2 and optionally $R^{2'}$ is not hydrogen, a protecting group, such as ^{t}butyloxycarbonyl is introduced as R^1 before the reduction of the nitro group, by methods known to the chemist skilled in the art. This protecting group is cleaved after the introduction of R^2 and optionally $R^{2'}$ by known methods.

Compounds of the general formulae IIa and IIIa are prepared by standard methods known to chemists skilled in the art as outlined below:

Reduction of a carboxylic acid ester with an appropriate reducing agent, such as diisobutyl aluminium hydride, followed by oxidation of the resulting benzylic alcohol with a suitable oxidant, such as tetrapropylammonium perruthenate/N-methylmorpholin-N-oxide, pyridinium chlorochromat, dimethylsulfoxide/ oxalylchloride. Alternatively, compounds of the general formulae II and III can be prepared by formylation reactions with dichloromethyl metyl ether and titanium

tetrachloride (Gross et al, *Org. Synth. Coll.*1973 Vol V, 365; Fanghaenel et al. *J. Prakt. Chem.* 1997, *339*, 277) Alternatively, compounds of the general formulae II and III can be prepared by methods known to chemists skilled in the art, such as deprotonation of a heteroaromatic compound with a strong base, such as alkyllithium, and subsequent reaction with N,N-dimethylformamide. Alternatively, compounds of the general formulae II and III can be prepared by methods known to chemists skilled in the art, such as halogen metal exchange reaction of halogen substituted heteroaromatic compounds, such as bromides or iodides, by the reaction with a metalating reagent, such as alkyllithium or alkylmagnesium halide or dialkylmagnesium. Alternatively, compounds of the general formulae II and III can be prepared by methods known to chemists skilled in the art, such as reaction of thiophenes and benzothiophenes with phosphoryl chloride in the presence of *N*-methyl-*N*-phenyl formamide (King et al. *J. Org. Chem.* 1949, *14*, 638) or *N,N*-dimethylformamide (Vilsmeier formylation, Raimundo et al. *J. Org. Chem.* 2002, *67*, 205).

Examples

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 µm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.

Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 µm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as

internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

For ion-exchange chromatography, the following material was used: SCX-columns (1 g) from Varian Mega Bond Elut®, Chrompack cat. No. 220776. Prior to use, the SCX-columns were pre-conditioned with 10% solution of acetic acid in methanol (3 mL). For de-complexation by irradiation, a ultaviolet light source (300 W) from Philipps was used. As starting polymer supports for solid phase synthesis, Wang-resin (1.03 mmol/g, Rapp-Polymere, Tuebingen, Germany) was used.

Preparation of intermediates

(4-Amino-phenyl)-carbamic acid ethyl ester.

4-Nitro-aniline (100 g, 0.72 mol) is dissolved in ethyl acetate (800 mL) and diisopropylethylamine (89.6 mL, 0.936 mol) is added. Ethyl chloroformiate (252 mL, 1.45 mol) dissolved in ethyl acetate (200 mL) is added and the solution is stirred for 18 h at ambient temperature. The mixture is washed with 2M HCl (300 mL) and brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo* to half of the original volume. To the resulting solution is added palladium on activated carbon (10 g, 5% Pd, 50 % H_2O) and the mixture is hydrogenated on a Parr apparatus (pH_2 = 3 bar) at ambient temperature for 12 h. The mixture is filtered through Celite and the solvent evaporated *in vacuo* to give 118 g (90 %) of the title compound as crystalline product. LC/MS (*m/z*) 180.9 (MH^+); t_R = 0.60 min. ^1H NMR ($CDCl_3$): 1.27 (t, 3H); 3.42 (br s, 2H, NH_2); 4.19 (q, 2H); 6.52 (br s, 1H NH); 6.64 (m, 2H); 7.14 (m, 2H).

(4-Phtalimido-phenyl)-carbamic acid ethyl ester.

(4-Amino-phenyl)-carbamic acid ethyl ester (118 g, 0.65 mol) is dissolved in glacial acetic acid (2.0 L) under nitrogen and the mixture is heated to 90 °C. Phthalic anhydride (102.0 g, 0.69 mol) is added portionwise over 30 min and the reaction is kept at 90 °C for 2 h. The mixture is allowed to cool to ambient temperature and the

precipitated solid is filtered off. The solid is washed on the filter with water (2 L) followed by diethylether (3 L) and then dried *in vacuo*. Yield 127g (62%) title compound as white crystalline compound. LC/MS (*m/z*) 311.3 (MH^+); t_R = 2.57 min. ^1H NMR (DMSO-d_6): 1.26 (t, 3H); 4.15 (q, 2H); 7.34 (dd, 2H); 7.58 (dd, 2H); 7.90 (ddd, 2H); 7.95 (ddd, 2H); 9.80 (s, 1H, NH).

(2-Nitro-4-phtalimido-phenyl)-carbamic acid ethyl ester.

(4-Phtalimido-phenyl)-carbamic acid ethyl ester (99.0 g, 0.32 mol) is suspended in glacial acetic acid (1.5 L) and heated to 90 °C. Fuming nitric acid (17.2 mL, 0.41 mol) is added dropwise over 30 min at 90-95 °C. The reaction mixture is then stirred at 100 °C for 1 h and cooled to ambient temperature. Crystallised solids are filtered off and washed with glacial acetic acid (500 mL), water (1 L) and diethylether (1 L) on the filter, then dried *in vacuo* to furnish 101 g (90 %) of the title compound as a yellow solid. LC/MS (*m/z*) 355.0 (MH^+); t_R = 3.34 min. ^1H NMR (DMSO-d_6): 1.25 (t, 3H); 4.16 (q, 2H); 7.81 (m, 2H); 7.93 (ddd, 2H); 7.99 (ddd, 2H); 6.15 (dd, 1H); 9.99 (s, 1H, NH).

(4-Amino-2-nitro-phenyl)-carbamic acid ethyl ester.

1,2-Dimethoxyethane (1.0 L) is added to (2-nitro-4-phtalimido-phenyl)-carbamic acid ethyl ester (101 g, 0.28 mol) and the mixture is heated under reflux. Hydrazine monohydrate (19.6 g, 0.39 mol) is added dropwise over 10 min and the mixture is stirred at reflux for 1.5 h. Upon cooling to ambient temperature the mixture is filtered and the solids are washed with dimethoxyethane (250 mL) on the filter. The filtrate is concentrated by means of evaporation and the red crystalline product is recrystallized from toluene (350 mL), precipitated product is filtered off and dried *in vacuo*. The mother liquor is concentrated to half the original volume and left standing for 16 h. Precipitated material is filtered off and recrystallized as before. The recrystallized solids are combined to furnish a total of 57.6 g (90 %) dark red title compound. LC/MS (*m/z*) 225.1 (MH^+); t_R = 2.08 min. ^1H NMR ($CDCl_3$): 1.33 (t, 3H); 3.77 (s, 2H, NH_2); 4.23 (q, 2H); 6.98 (dd, 1H); 7.45 (d, 1H); 8.28 (d, 1H); 9.39 (s, 1H, NH).

[4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophen-2-yl]-methanol.

A solution of 4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophene-2-carboxylic acid methyl ester (992 mg, 3.00 mmol) in dry THF (20 mL) and dry CH_2Cl_2 (10 mL) was cooled to 0 °C under N_2, and DIBAL-H (9.0 mL, 9.0 mmol, 1 M solution in toluene) was added. After 3 h, another portion of DIBAL-H (4.5 mL, 4.5 mmol) was added, and stirring was continued for another 2 h. The reaction was quenched by the addition of sat. Rochelle salt solution (30 mL), and the mixture was stirred for 1 h at room temperature. The phases were separated, the aqueous phase was extracted with EtOAc (2 × 50 mL) and the pooled organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by chromatography on silica gel on a FlashMaster system using as eluent heptane/ethyl acetate (linear gradient elution from 1:0 to 6:4). Fractions containing the product were pooled and evaporated *in vacuo* to yield the desired compound (788 mg, 87%).

LC-MS: $m/z = 285.2$ ($M-H_2O+H^+$), calcd for $C_{12}H_{10}ClO_2S_2$: 284.9805, $t_R = 2.45$ min.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.84 (t, $J = 5.7$ Hz, 1 H), 2.20 (s, 3 H), 4.73 (d, $J = 5.7$ Hz, 2 H), 7.49 (d, $J = 8.5$ Hz, 2 H), 7.84 (d, $J = 8.5$ Hz, 2 H), 8.18 (s, 1 H).

The following compound was prepared analogously:

(3-Chloro-thiophen-2-yl)-methanol.

Yield: 73%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92 (br s, 1 H), 4.81 (s, 2 H), 6.91 (d, $J =$ 5.2 Hz, 1 H), 7.25 (d, $J = 5.2$ Hz, 1 H).

(4-Bromo-3-methoxy-thiophen-2-yl)-methanol.

A suspension of 4-bromo-3-hydroxy-thiophene-2-carboxylic acid methyl ester (948 mg, 4.00 mmol), dimethyl sulphate (0.57 mL, 6.0 mmol), and K_2CO_3 (1.11 g, 8.0 mmol) in acetone (10 mL) was heated under reflux for 4 h. After cooling to room temperature, water (25 mL) was added. The mixture was extracted with EtOAc (2 × 25 mL), and the extracts were pooled, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in dry THF (20 mL), the solution was cooled to 0 °C under N_2, and DIBAL-H (12 mL, 12 mmol, 1 M solution in toluene) was added. After 2 h, another portion of DIBAL-H (6 mL, 6 mmol) was added, and stirring was continued for another 2 h. The reaction was quenched by the addition of sat. Rochelle salt solution (30 mL), and the mixture was stirred for 1 h at room temperature. The phases were separated, the aqueous phase was extracted with EtOAc (2 × 50 mL) and the

pooled organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by chromatography on silica gel on a FlashMaster system using as eluent heptane/ethyl acetate (linear gradient elution from 1:0 to 2:1). Fractions containing the product were pooled and evaporated *in vacuo* to yield the desired compound (482 mg, 54%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (br s, 1 H), 3.90 (s, 3 H), 4.77 (s, 2 H), 7.15 (s, 1 H).

The following compound was prepared analogously:

(6-Chloro-3-methoxy-benzo[b]thiophen-2-yl)-methanol.

Yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92 (t, J = 5.9 Hz, 1 H), 3.99 (s, 3 H), 4.90 (d, J = 5.7 Hz, 2 H), 7.33 (dd, J = 1.9, 8.5 Hz, 1 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.73 (d, J = 1.9 Hz, 1 H).

Preparation of heteroaryl aldehydes of the general formula IIa and IIIa

4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophene-2-carbaldehyde.

To a suspension of [4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophen-2-yl]-methanol (786 mg, 2.60 mmol), 4-methylmorpholine *N*-oxide (0.46 g, 3.9 mmol), and powdered 4 Å molecular sieves (1.3 g, activated by brief heating *in vacuo*) in CH_2Cl_2 (7 mL) was added tetrapropylammonium perruthenate (46 mg, 0.13 mmol). The resulting mixture was stirred for 1 h, after which it was filtered through a plug of silica (ca. 25 g) eluting with EtOAc. The eluate was evaporated *in vacuo* and the product was purified by chromatography on silica gel on a FlashMaster system using as eluent heptane/ethyl acetate (linear gradient elution from 1:0 to 1:1). Fractions containing the product were pooled and evaporated *in vacuo* to yield the title compound (644 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$): δ2.60 (s, 3 H), 7.53 (d, J = 9.0 Hz, 2 H), 7.87 (d, J = 8.5 Hz, 2 H), 8.53 (s, 1 H), 10.01 (s, 1 H).

The following aldehydes were prepared analogously:

3-Chloro-thiophene-2-carbaldehyde.

Yield: 94%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, J = 5.2 Hz, 1 H), 7.72 (d, J = 0.5, 4.7 Hz, 1 H), 10.07 (d, J = 0.9 Hz, 1 H).

4-Bromo-3-methoxy-thiophene-2-carbaldehyde.

Yield: 45%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.18 (s, 3 H), 7.60 (d, J = 1.4 Hz, 1 H), 10.08 (d, J = 1.4 Hz, 1 H).

6-Chloro-3-methoxy-benzo[b]thiophene-2-carbaldehyde.

Yield: 86%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.34 (s, 3 H), 7.36 (dd, J = 1.7, 8.7 Hz, 1 H), 7.75 (d, J = 1.4 Hz, 1 H), 7.82 (d, J = 8.5 Hz, 1 H), 10.36 (s, 1 H).

5-Fluoro-benzofuran-3-carbaldehyde.

At a constant temperature of –60 °C dimethylsulfoxide (3.27 g, 41.8 mmol) in dichloromethane (10 mL) was added to a solution of oxalylchloride (2.65 g, 20.9 mmol) in dichloromethane (30 mL) and the solution was stirred for 15 minutes. 1-(5-Fluorobenzofuran-3-yl)methanol (3.16 g, 19.0 mmol) dissolved in dichloromethane (60 mL) was added dropwise at –60 °C. The mixture was stirred for 20 minutes followed by addition of triethylamine (9.61 g, 0.095 mmol). After stirring for 10 minutes, the reaction mixture was allowed to heat to ambient temperature and stirred for additional 20 minutes. The organic fraction was washed successively with 50 mL portions of water, 1N aqueous HCl, saturated aqueous sodium bicarbonate and brine, then dried ($MgSO_4$) and concentrated *in vacuo* to furnish crude title compound in quantitative yield as a beige crystalline solid.

^{1}H NMR ($CDCl_3$): 7.13 (dt, 1H); 7.50 (dd, 1H); 7.86 (dd, 1H); 8.30 (s, 1H); 10.15 (s, 1H).

Preparation of intermediates of general formula IV

Intermediates of the general formula IV were prepared by a general method as described below for the preparation of {4-[(5-Fluoro-benzofuran-3-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester.

{4-[(5-Fluoro-benzofuran-3-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester.

In a 3-necked round bottomed flask fitted with a Dean-Stark apparatus 5-Fluoro-benzofuran-3-carbaldehyde (3.59 g, 21.9 mmol) and (4-amino-2-nitro-phenyl)-carbamic acid ethyl ester (4.48 g, 19.9 mmol) were mixed in o-xylene (80 mL) and a catalytic amount of acidic ion exchange resin (Amberlite IRC-84, 100 mg) was added. The mixture was heated to reflux for 5 h, filtered warm and concentrated *in vacuo*. This crude product was dissolved in a dioxane:methanol (4:1) mixture (90 mL) and sodiumborohydride (1.50 g, 39.8 mmol) was added portionwise over a period of 30 minutes. The reaction mixture was stirred at ambient temperature over night, then poured into water (200 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and evaporated to give a crude solid which was purified by chromatography on silica gel (eluent: ethyl acetate:heptane 1:2). This furnished 4.50 g (61 %) of the title compound as a red crystalline material.

^{1}H NMR (CDCl3): 1.33 (t, 3H); 4.07 (t, 1H); 4.23 (q, 2H); 4.42 (d, 2H); 6.99 (dd, 1H); 7.05 (dt, 1H); 7.25 (dd, 1H); 7.42 (t, 1H); 7.44 (d, 1H); 7.65 (s, 1H); 8.31 (d, 1H); 9.39 (s, 1H).

The following intermediates were prepared analogously:

{4-[(5-methyl-thiophen-2-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester
Yield: 73%. LC/MS (*m/z*) 336 (MH^+); t_R = 3.41 min.

{4-[(3-methyl-thiophen-2-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester
Yield: 89%. LC/MS (*m/z*) [MBN]

{4-[(thiophen-2-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester
Yield: 71%. LC/MS (*m/z*) 321 (MH^+); t_R = 3.24 min.

{4-[(thiophen-3-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester
Yield: 69%. LC/MS (*m/z*) 320 (MH^+); t_R = 3.08 min.

Compounds of the invention

Example 1

1a {2-Amino-4-[(5-fluoro-benzofuran-3-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester.

{4-[(5-Fluoro-benzofuran-3-ylmethyl)-amino]-2-nitro-phenyl}-carbamic acid ethyl ester (4.50 g, 12.1 mmol) was dissolved in abs. ethanol (140 mL) whereto 6N aqueous HCl (38 mL) and iron powder (5.70 g, 0.10 mol) was added. The red mixture was heated at 60 °C until the intense colour disappeared (20 minutes). The solids were filtered off and the ethanol was removed from the filtrate by evaporation *in vacuo*. Aqueous ammonia (sat.) was added to the remanence, which was then extracted with ethyl acetate (3 x 100 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (eluent: ethyl acetate:heptane 1:1) to furnish 2.70 g (66 %) of the title compound as a solid. M.p. 150-151 °C. Calculated for $C_{18}H_{18}FN_3O_3$: C 62.96; H 5.28; N 12.24. Found: C 63.00; H 5.38; N 12.13. LC/MS (*m/z*) 344 (MH^+); t_R = 2.00 min. ^1H NMR (DMSO-d_6): 1.19 (t, 3H); 4.03 (q, 2H); 4.26 (d, 2H); 4.55 (s, 2H, NH2); 5.79 (t, 1H); 5.91 (dd, 1H); 6.02 (d, 1H, NH); 6.72 (d, 1H); 7.13 (dt, 1H); 7.56 (m, 2H); 7.95 (s, 1H); 8.16 (br s, 1H, NH).

The following compounds were prepared analogously:

1b {2-Amino-4-[(5-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester dihydrochloride

M.p. 190°C (dec.). Calculated for $C_{15}H_{19}N_3O_2S,2HCl$: C 47.00; H 5.67; N 10.97. Found: C 46.84; H 5.86; N 11.10. LC/MS (*m/z*) 306 (MH^+); t_R = 1.77 min. ^1H NMR (DMSO-d_6): 1.22 (t, 3H); 2.37 (s, 3H); 4.08 (q, 2H); 4.37 (s, 2H); 6.64 (m, 1H); 6.67 (dd, 1H); 6.72 (d, 1H); 6.86 (d, 1H); 7.13 (d, 1H); 8.93 (br s, 1H, NH).

1c {2-Amino-4-[(3-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester dihydrochloride

LC/MS (*m/z*) 306 (MH^+); t_R = 1.68 min. ^1H NMR ($CDCl_3$) (free base): 1.25 (t, 3H); 2.23 (s, 3H); 3.78 (br s, 3H); 4.13 (q, 2H); 4.32 (s, 2H); 6.05-6.10 (m, 2H + NH); 6.82 (d, 1H); 6.93 (d, 1H); 7.11 (d, 1H).

1d {2-Amino-4-[(thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester dihydrochloride

M.p. 195°C. Calculated for $C_{14}H_{17}N_3O_2S,2HCl$: C 46.16; H 5.26; N 11.54. Found: C 46.34; H 5.43; N 11.28. LC/MS (*m/z*) 292 (MH^+); t_R = 1.58 min. ^1H NMR (DMSO-d_6): 1.22 (t, 3H); 4.08 (q, 2H); 4.48 (s, 2H); 6.71 (dd, 1H); 6.79 (d, 1H); 6.97 (dd, 1H); 7.10 (d, 1H); 7.16 (d, 1H); 7.40 (d, 1H); 8.97 (br s, 1H, NH).

1e {2-Amino-4-[(thiophen-3-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester dihydrochloride

M.p. 196-197°C. Calculated for $C_{14}H_{17}N_3O_2S,2HCl$: C 46.16; H 5.26; N 11.54. Found: C 46.23; H 5.47; N 11.30. LC/MS (*m/z*) 292 (MH^+); t_R = 1.54 min. ^1H NMR (DMSO-d_6): 1.21 (t, 3H); 4.08 (q, 2H); 4.29 (s, 2H); 6.66 (dd, 1H); 6.73 (d, 1H); 7.14 (dd, 1H); 7.16 (d, 1H); 7.45 (m, 1H); 7.51 (dd, 1H); 8.86 br s, 1H, NH).

Example 2

2a (2-Amino-4-{[4-(4-chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-phenyl)-carbamic acid ethyl ester

A suspension of 4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophene-2-carbaldehyde (301 mg, 1.00 mmol) and (4-amino-2-nitro-phenyl)-carbamic acid ethyl ester (293 mg, 1.30 mmol) in abs. ethanol (10 mL) was heated under reflux for 20 h under N_2. After cooling, the orange to red solid imine formed was collected by filtration and vacuum dried to yield a crude product (312 mg, 61%), which was suspended in methanol:acetic acid 10:1 (10 mL). $NaBH_3CN$ (0.19 g, 3.0 mmol) was added and the mixture was stirred for 1 h at room temperature. Then another portion of $NaBH_3CN$ (0.19 g, 3.0 mmol) was added, and after further 1 h, saturated aqueous sodium bicarbonate (20 mL) was added. The red solid amine formed was collected by filtration and vacuum dried to yield a crude product (293 mg, 94 %) which was suspended in absolute ethanol (10 mL). To this was added 6 N HCl (1.1 mL, 6.6 mmol) and iron powder (193 mg, 3.46 mmol), and the red mixture was heated to 60 °C until the red color had faded to yellow, *ca.* 10-20 minutes. The mixture was poured into saturated aqueous sodium bicarbonate (50 mL) and EtOAc (50 mL), the resulting mixture was filtered, the phases were separated, and the aqueous phase was further extracted with EtOAc (2 × 50 mL). The combined organic phases were dried

(Na_2SO_4) and the solvents evaporated *in vacuo*. The product was purified by chromatography on silica gel on a FlashMaster system using as eluent heptane/ethyl acetate (linear gradient elution, typically from 8:2 to 1:1). The fractions containing the product were pooled and evaporated *in vacuo* to yield the title compound as a pale yellow solid (213 mg, 78%).

LC-MS: m/z = 480.1 ($M+H^+$), calcd for $C_{21}H_{23}ClN_3O_4S_2$: 480.0813, t_R = 2.35 min, UV purity = 72.4%, ELS purity = 86.5%. ^1H NMR (500 MHz, DMSO-d_6): δ 1.19 (br s, 3 H), 2.16 (s, 3 H), 4.02 (q, J = 6.9 Hz, 2 H), 4.23 (d, J = 6.1 Hz, 2 H), 4.57 (s, 2 H), 5.81 (dd, J = 2.4, 8.5 Hz, 1 H), 5.91-5.95 (m, 2 H), 6.72 (br d, J = 6.6 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.90 (d, J = 8.5 Hz, 2 H), 8.15 (br s,), 8.31 (s, 1 H).

The following compounds were prepared analogously:

2b {2-Amino-4-[(3-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester

Yield: 76%. LC-MS: m/z = 326.0 ($M+H^+$), calcd for $C_{14}H_{17}ClN_3O_2S$: 326.0725, t_R = 1.95 min, UV purity = 85.8%, ELS purity = 98.1%. ^1H NMR (500 MHz, DMSO-d_6): δ 1.19 (br s, 3 H), 4.03 (q, J = 7.1 Hz, 2 H), 4.30 (d, J = 6.1 Hz, 2 H), 4.57 (s, 2 H), 5.83 (dd, J = 2.4, 8.5 Hz, 1 H), 5.93-5.97 (m, 2 H), 6.73 (br d, J = 7.1 Hz, 1 H), 6.99 (d, J = 5.2 Hz, 1 H), 7.48 (d, J = 5.2 Hz, 1 H), 8.16 (br s, 1 H).

2c {2-Amino-4-[(4-bromo-3-methoxy-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester

Yield: 66%. LC-MS: m/z = 402.0 ($M+H^+$), calcd for $C_{15}H_{19}BrN_3O_3S$: 400.0325 (100%), 402.0310 (97.3%), t_R = 1.97 min, UV purity = 87.9%, ELS purity = 98.2%. ^1H NMR (500 MHz, DMSO-d_6): δ 1.20 (br s, 3 H), 3.83 (s, 3 H), 4.03 (q, J = 6.9 Hz, 2 H), 4.32 (d, J = 6.1 Hz, 2 H), 4.58 (s, 2 H), 5.84-5.89 (m, 2 H), 5.97 (d, J = 2.4 Hz, 1 H), 6.74 (br s, 1 H), 7.46 (s, 1 H), 8.17 (br s, 1 H).

2d {2-Amino-4-[(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester

Yield: 60%. LC-MS: m/z = 405.3 ($M+H^+$), calcd for $C_{19}H_{21}ClN_3O_3S$: 406.0987, t_R = 2.39 min, UV purity = 95.0%, ELS purity = 99.6%. ^1H NMR (500 MHz, DMSO-d_6): δ 1.19 (br s, 3 H), 3.95 (s, 3 H), 4.02 (q, J = 7.1 Hz, 2 H), 4.43 (d, J = 6.1 Hz, 2 H),

4.56 (s, 2 H), 5.90 (dd, J = 2.4, 8.5 Hz, 1 H), 5.96 (t, J = 5.9 Hz, 1 H), 6.00 (d, J = 2.8 Hz, 1 H), 6.73 (br d, J = 6.6 Hz, 1 H), 7.39 (dd, J = 1.9, 8.5 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.98 (d, J = 1.9 Hz, 1 H), 8.15 (br s, 1 H).

Example 3

3a {2-Amino-4-[(5-methyl-thiophen-2-ylmethyl)-(methyl) -amino]-phenyl}-carbamic acid ethyl ester

A mixture of 5-methyl-2-thiophenecarboxaldehyde (108 µL, 1.00 mmol), (4-amino-2-nitro-phenyl)-carbamic acid ethyl ester (225 mg, 1.00 mmol) and Amberlite IRC-84 (10 mg) in *o*-xylene (4 mL) was heated at reflux under Ar for 5 h. Volatiles were removed by evaporation *in vacuo*, and the residue was dissolved in acetonitrile (5 mL). To the resulting solution was added $NaBH_3CN$ (0.25 g, 4.0 mmol) followed by HOAc (5 drops). After stirring for 5 minutes, the solution became dark red. Formaldehyde (37 % solution in water, 0.89 mL, 12 mmol) was added, and stirring was continued for 30 minutes. with occasional addition of. The reaction mixture was evaporated to dryness *in vacuo* and the residue was partitioned between saturated aqueous sodium bicarbonate (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (50 mL) and the combined organic layers were dried (Na_2SO_4) and the solvents evaporated *in vacuo*. The residue was then dissolved in ethanol (10 mL). 6 N aqueous HCl (2.0 mL, 12 mmol) and iron powder (0.34 g, 6.0 mmol) were added, and the red mixture was heated at 60 °C until the red color had faded to yellow, *ca.* 15 min. The mixture was poured into saturated aqueous sodium bicarbonate (50 mL) and EtOAc (50 mL), the resulting mixture was filtered, the phases were separated, and the aqueous phase was further extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvents evaporated *in vacuo*. The product was purified by chromatography on silica gel on a FlashMaster system using as eluent heptane/ethyl acetate (linear gradient elution, typically from 8:2 to 1:1). The fractions containing the product were pooled and evaporated *in vacuo* to yield the title compound as a pale yellow solid (145 mg, 45% overall).

LC-MS: m/z = 319.9 ($M+H^+$), calcd for $C_{16}H_{22}N_3O_2S$: 320.1427, t_R = 1.80 min, UV purity = 98.4%, ELS purity = 97.2%. ^1H NMR (250 MHz, $CDCl_3$): δ 1.29 (t, J = 7.1,

3 H), 2.41 (s, 3 H), 2.91 (s, 3 H), 3.76 (br s, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.52 (s, 2 H), 6.02 (br s, 1 H), 6.17 (d, J = 2.8 Hz, 1 H), 6.25 (dd, J = 2.8, 8.5 Hz, 1 H), 6.53-6.58 (m, 1 H), 6.66 (d, J = 3.3 Hz, 1 H), 6.98 (d, J = 8.5 Hz, 1 H).

The following compound was prepared analogously:

***3b** {2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)-amino]-phenyl}-carbamic acid ethyl ester*

Yield: 34%. LC-MS: m/z = 340.0 ($M+H^+$), calcd for $C_{15}H_{19}ClN_3O_2S$: 340.0881, t_R = 2.14 min, UV purity = 82.3%, ELS purity = 90.2%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (t, J = 6.8, 3 H), 2.91 (s, 3 H), 3.78 (br s, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.49 (s, 2 H), 6.05 (br s, 1 H), 6.16 (d, J = 2.4 Hz, 1 H), 6.24 (dd, J = 2.4, 8.5 Hz, 1 H), 6.73 (d, J = 3.8 Hz, 1 H), 6.99 (d, J = 8.5 Hz, 1 H).

The following compound was prepared analogously, except that formaldehyde was substituted for acetaldehyde:

***3c** {2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-(ethyl)-amino]-phenyl}-carbamic acid ethyl ester*

Yield: 12%. LC-MS: m/z = 353.9 ($M+H^+$), calcd for $C_{16}H_{21}ClN_3O_2S$: 354.1038, t_R = 2.02 min, UV purity = 97.5%, ELS purity = 99.0%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (t, J = 7.1, 3 H), 1.29 (t, J = 6.8, 3 H), 3.36 (q, J = 7.1 Hz, 2 H), 3.76 (br s, 2 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.47 (s, 2 H), 6.05 (br s, 1 H), 6.13 (d, J = 2.4 Hz, 1 H), 6.19 (dd, J = 2.4, 9.0 Hz, 1 H), 6.73 (d, J = 3.8 Hz, 1 H), 6.96 (d, J = 8.0 Hz, 1 H).

Example 4

***4a** {2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester*

A solution of 5-chlorothiophene-2-carbaldehyde (240 µL, 111 µmol, 463 mM in 1,2-dichloroethane) was added to a solution of 4-amino-2-nitrophenylcarbamic acid ethyl ester (240 µL, 111 µmol, 463 mM in 1,2-dichloroethane). Sodium triacetoxyborohydride (118 mg, 555 µmol) was added, and the resulting mixture was stirred for 3.5 hours at 40 °C. The mixture was allowed to cool to ambient temperature, and water (100 µL) was added. The mixture was filtered through silica gel (500 mg) and the column was washed with 1,2-dichloroethane (3 mL). The

combined organic phases were evaporated to dryness *in vacuo*. The resulting solid was dissolved in ethanol (3 mL). Iron (19 mg) was added to one-third of the resulting solution (1 mL), followed by an aqueous solution of hydrochloric acid (96 µL, 6M). The resulting mixture was placed in an ultrasonic bath for 10 minutes. Then, saturated aqueous sodium bicarbonate solution (2 mL) was added. The mixture was extracted with ethyl acetate (3 mL). The organic phase was washed with water (3 mL) and brine (3 mL), dried over magnesium sulphate, filtered, and evaporated to dryness *in vacuo*. The resulting product was dissolved in 190 µL dimethylsulfoxide and subjected to preparative LC-MS purification. The resulting solution was evaporated to dryness *in vacuo*. Yield (6.8 mg, 56%). LC-MS (m/z) $(M+H)^+$ 326.1 RT=1.90 (UV, ELSD) 92%, 99%.

The following compounds were prepared in an analogous fashion:

4b {2-Amino-4-[(5-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester
LC-MS (m/z) $(M+H)^+$ 371.9 RT=1.94 (UV, ELSD) 89%, 98%.

4c {2-Amino-4-[(4-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester
LC-MS (m/z) $(M+H)^+$ 372.0 RT=1.96 (UV, ELSD) 76%, 100%.

4d {2-Amino-4-[(5-ethyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester
LC-MS (m/z) $(M+H)^+$ 320.1 RT=1.90 (UV, ELSD) 72%, 96%.

4e {2-Amino-4-[(benzo[b]thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester
LC-MS (m/z) $(M+H)^+$ 342.1 RT=2.06 (UV, ELSD) 75%, 100%.

4f {2-Amino-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester
LC-MS (m/z) $(M+H)^+$ 368.2 RT=2.21 (UV, ELSD) 90%, 99%.

In vitro and in vivo testing

The compounds of the invention have been tested and shown effect in one or more of the below models:

Relative efflux through the KCNQ2 channel.

Cells stably expressing voltage-gated KCNQ2 channels were seeded on the day before the experiment and loaded with [^{86}Rb]. On the day of the experiment cells were washed with a HBSS-containing buffer. Cells were preincubated with drug and the [^{86}Rb+] was stimulated by a submaximal concentration of 15 mM KCl in the continued presence of drug. After a suitable incubation period, the supernatant was removed and counted in a liquid scintillation counter (Tricarb). Cells were lysed with 2 mM NaOH and the amount of ^{86}Rb+ was counted. The relative efflux was calculated $((CPM_{super}/CPM_{super}+ CPM_{cell})_{Cmpd}/ (CPM_{super}/CPM_{super}+ CPM_{cell})_{15mM\ KCl})*100-100$.

The compounds of the invention have an EC_{50} of less than 20000, in most cases less than 2000 and in many cases less than 200. Accordingly, the compounds of the invention are useful in the treatment of diseases associated with the KCNQ family potassium channels.

Maximum electroshock

The test was conducted in groups of male mice using corneal electrodes and administering a square wave current of 26mA for 0.4seconds in order to induce a convulsion characterised by a tonic hind limb extension (Wlaz et al. *Epilepsy Research* 1998, 30, 219-229).

Pilocarpine induced seizures

Pilocarpine induced seizures are induced by intraperitoneal injection of pilocarpine 250mg/kg to groups of male mice and observing for seizure activity resulting in loss of posture within a period of 30 minutes (Starr et al. *Pharmacology Biochemistry and Behavior* 1993, 45, 321-325)

Threshold test

The threshold dose of pentylenetetrazole required to induce a cronic convulsion was measured by timed infusion of pentylenetetrazole (5mg/ml at 0.5 ml/min) into a

lateral tail vein of groups of male mice (Nutt et al. *J Pharmacy and Pharmacology* 1986, 38, 697-698).

Side effects

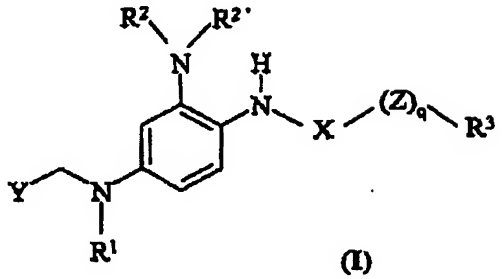
Central nervous system side-effects were measured by measuring the time mice would remain on rotarod apparatus (Capacio et al. *Drug and Chemical Toxicology* 1992, 15, 177-201).

Pharmacokinetics

The pharmacokinetic properties of the compound were determined via. i.v. and p.o. dosing to Spraque Dawley rats, and, thereafter, drawing blood samples over 20 h. Plasma concentrations were determined with LC/MS/MS.

Claims

1. A 1,2,4-triaminobenzene derivative of formula I



(I)

wherein

R^1 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl;

R^2 and $R^{2'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, aryl, , C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

R^3 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, aryl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

X is CO or SO_2;

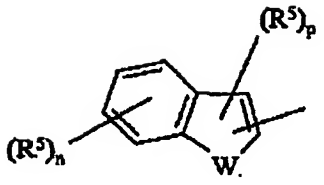
Z is O or NR^4, wherein R^4 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

q is 0 or 1;

and

Y represents a heteroaryl of formula II or III

II



III

wherein

W is O or S;

m is 0,1, 2 or 3;

n is 0, 1, 2, 3 or 4;

p is 0 or 1; and

each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, aryl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl-C_{1-6}-alk(en/yn)yl, acyl, halogen, halo-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8, SO_2OR^8;

wherein

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and aryl;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl and acyl; and

R^8 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, aryl and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl

or pharmaceutically active acid addition salts thereof.

2. A compound according to claim 1 wherein R^1 is selected from the group consisting of hydrogen and C_{1-6}-alk(en/yn)yl.

3. A compound according to any of claims 1 and 2 wherein at least one of the substituents R^2 and $R^{2'}$ is a hydrogen atom

4. A compound according to any of claims 1-3 wherein both R^2 and $R^{2'}$ are hydrogen atoms.

5. A compound according to any of claims 1-4 wherein R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl and aryl-C_{1-6}-alk(en/yn)yl.

6. A compound according to any of claims 1-5 wherein R^3 is C_{1-6}-alk(en/yn)yl.

7. A compound according to any of claims 1-6 wherein each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, halogen and $-SO_2R^8$ wherein R^8 is aryl.

8. A compound according to any of claims 1-7 wherein X is CO.

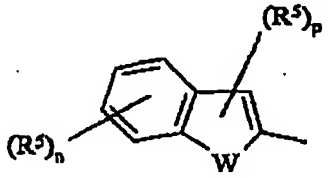
9. A compound according to any of claims 1-8 wherein Z is an oxygen atom.

10. A compound according to any of claims 1-9 wherein W is an oxygen atom.

11. A compound according to any of claims 1-10 wherein W is a sulfur atom.

12. A compound according to any of claims 1-11 wherein Y is of formula IIb or IIIb

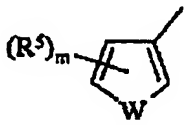
IIb



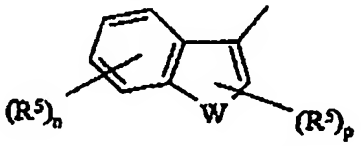
IIIb

wherein W, m, n, p and R^5 are as defined above.

13. A compound according to any of claims 1-11 wherein Y is of formula IIc or IIIc



IIb



IIIb

wherein W, m, n, p and R^5 are as defined above.

14. A compound according to any of claims 1-13 wherein Y is of formula II.

15. A compound according to any of claims 1-14 wherein Y is of formula III.

16. A compound according to any of claims 1-15, said compound being selected from the group consisting of:
{2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-methyl-amino]-phenyl}-carbamic acid ethyl ester;
{2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;
{2-Amino-4-[(5-methyl-thiophen-2-ylmethyl)-methyl-amino]-phenyl}-carbamic acid ethyl ester;
{2-Amino-4-[(5-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(benzo[b]thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(5-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(4-bromo-3-methoxy-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(3-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

(2-Amino-4-{[4-(4-chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-phenyl)-carbamic acid ethyl ester;

{2-Amino-4-[(3-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(5-fluoro-benzofuran-3-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(4-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(5-ethyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(thiophen-3-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester;

{2-Amino-4-[(5-chloro-thiophen-2-ylmethyl)-ethyl-amino]-phenyl}-carbamic acid ethyl ester;

or a pharmaceutically acceptable acid addition salt thereof;

17. A pharmaceutical composition comprising a compound according to any of the claims 1-16 in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

18. Use of a compound of any of claims 1-17 for the manufacture of a pharmaceutical preparation for the prevention, treatment or inhibition of a disorder of the central nervous system.

19. Use according to claim 18 characterized in that the disorder is selected from the group consisting of seizure disorders, neuropathic pain, anxiety disorders, neurodegenerative disorders and neuronal hyperexcitation states.

20. Use according to claim 19 characterized in that the seizure disorder is convulsions, epilepsy or status epilepticus.

21. Use according to claim 19 characterized in that the neuropathic pain is allodynie, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie or neupathic pain related to migraine.

22. Use according to claim 19 characterized in that the anxiety disorder is anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia or specific phobias.

23. Use according to claim 19 characterized in that the neurodegenerative disorder is alzheimer's disease, huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-induced encephalopathy or other infection-related encephalopathies being caused by rubella viruses, herpes viruses, borrelia or by unknown pathogens, Creutzfeld-Jakob disease, Parkinson's disease, trauma-induced neurodegenerations or neurodegenerative disorders of the peripheral nervous system such as polyneuropathies and polyneuritides.

24. Use according to claim 19 characterized in that the neuronal hyperexcitation state appears in medicament withdrawal or by intoxication.